## REMARKS/ARGUMENTS

This Submission of Request for Continued Examination is in response to the Office Action dated August 5, 2004 in connection with the above application. Issues raised in the Office Action are addressed below in the order they were raised by the Examiner.

Applicants note that the Amendment filed on May 24, 2004 has been entered. Claims 2, 9-12, 16, and 20-25 are pending.

Applicants note with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 102(e) and under 35 U.S.C. § 112, second paragraph, in view of Applicants' Response and Amendment filed on May 24, 2004.

Rejection of Claims 2, 9-12, 16, 20, and 24-25 under 35 USC § 103(a)

Claims 2, 9-12, 16, 20, and 24-25 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Uchida et al. (U.S. 6,150,092) and Robinson et al. (5,814,620; 5,710,136; and 5,801,156). In particular, the Examiner states that "[o]ne would clearly have had motivation to make the instantly claimed antisense molecule since it is absolutely clear that the region targeted has been clearly shown by the prior art [Uchida et al.] to be a desired target for antisense inhibition of VEGF. One in the art would clearly look to the SEQ ID NO: 7 region in the making of antisense targeted to VEGF and the optimization of antisense to VEGF, for example." See Office Action, the paragraph bridging pages 3 and 4. Applicants respectfully traverse this rejection. Applicants show below that the combination of references fails to (A) provide motivation or reasonable expectation of success; and fails to (B) provide the claimed invention.

A. Lack of Motivation & Reasonable Expectation of Success

In making the combination of the cited prior art, the Examiner appears to admit that Uchida et al. fail to describe any of the specific claimed antisense sequences which comprise a plurality of phosphorothioate moieties, but argues that because Robinson et al. disclose that "synthetic oligonucleotides of their invention [VEGF antisense] may be used in pharmaceutical preparation when combined with appropriate carrier, including liposomes . . . and phosphorothioate modifications," a skilled artisan would be motivated to modify Uchida's antisense molecules to include phosphorothioate moieties as taught by Robinson et al. (see

Office Action, at page 3). Applicants respectfully submit that this rejection is legally insufficient in that:

(a) there is no suggestion or motivation in the cited art to modify the sequence of any of Uchida's antisense molecules to arrive at the instantly claimed antisense molecules;

(b) there is no suggestion or motivation in the cited art to modify the instantly claimed antisense molecules to include phosphorothioate (PS) moieties; and

(c) there is no reasonable expectation leading one skilled in the art to believe that such a combination would result in PS-modified antisense molecules that are effective for use in vivo or in cells.

Applicants have previously addressed the deficiencies presented by the Uchida et al. and Robinson et al. in the Response and the unexecuted Declaration of Dr. Gill filed on May 24, 2004. Applicants note that the Examiner has refused to consider the unexecuted copy of the Declaration of Dr. Gill (Office Action, at page 6, lines 18-19). In response, Applicants submit herein an executed Declaration of Dr. Parkash Gill. Further, Applicants submit an executed Declaration of Dr. Ruiwen Zhang. Both Dr. Gill and Dr. Zhang are well known experts in the fields of antisense nucleic acids and cancer therapy, as evidenced in part by their publications. A copy of Dr. Zhang's CV is enclosed herewith, and a listing of Dr. Gill's publications in the antisense field is also enclosed herewith. While Dr. Gill is a named inventor on the present application, Dr. Zhang is an unrelated third party scientist. Applicants respectfully request the Examiner to enter and consider these two Declarations and to reconsider a fundamental issue in the prosecution of this application, that being whether the prior art is sufficient to establish a *prima facie* case for obviousness.

In making the present rejection, the Examiner has stated: "[o]ne would clearly have had motivation to make the instantly claimed antisense molecule since it is absolutely clear that the region targeted has been clearly shown by the prior art [Uchida et al.] to be a desired target for antisense inhibition of VEGF." This statement is clearly rebutted by the Declarations of Dr. Gill and Dr. Zhang, which, as discussed below, demonstrate that the data in Uchida et al. do not show any reliable information regarding the efficacy of the VEGF antisense probes in cells or in vivo.

Applicants stress that although Uchida et al. disclose a region that overlaps or encompasses certain claimed antisense nucleic acids, Uchida et al. fail to teach any of the exact antisense sequences or how to design their antisense sequences to arrive at the presently claimed nucleic acid sequences.

Assuming *arguendo*, a skilled artisan were to design antisense nucleic acids based on Uchida's disclosure, Applicants believe that there is no suggestion or motivation in the cited art to make the instantly claimed modified antisense nucleic acids as suggested by the Examiner. A close review of Uchida et al. shows that the unmodified antisense probes of Uchida are effective in suppressing VEGF gene expression in a cell-free biochemical assay (see, e.g., Uchida et al., Tables 1-8). However, none of the Uchida PS-modified antisense probes proved to be effective in cell-based assays or in vivo (see, e.g., Uchida et al., Table 9). As noted in the Declarations of Dr. Gill and Dr. Zhang, phosphorothioate modifications are employed only when an antisense probe is intended for use in cells or in vivo. Therefore, the unmodified probes described by Uchida et al. would not render obvious the instantly claimed PS-modified probes because Uchida's PS-modified probes were not effective in cells. It is Applicants' position that one of ordinary skill in the art, upon reviewing Uchida et al., would not be motivated to design antisense constructs based on Uchida's probes and further modify the probes with PS moieties as suggested by the Examiner because the cited prior art fails to provide any reasons for the skilled artisan to do so.

In rebuttal, Examiner asserts that "Applicant argue that the antisense modified by Uchida et al do not work well in cells. This is merely an opinion with no data . . . Applicant's argument as to the 'poor effectiveness' of the antisense of Uchida as compared to the antisense instantly claimed antisense has not been demonstrated" (see Office Action, at page 7-8). Applicants respectfully disagree.

Contrary to the Examiner's assertion, Uchida's data actually show that their PS-modified antisense probes do not work well in cells. As pointed out in the previous responses, Uchida et al. provide inconsistent results from cell free assays and cell-based assays. For example, all of the six PS-modified probes listed in Table 9 showed only mild effect on VEGF expression in the cell-based assay despite their strong effect in cell-free assays. See, e.g., Tables 1 and 9 of Uchida et al. To illustrate, while the unmodified probe A311 (SEQ ID NO: 51) of Uchida

inhibited 96% of VEGF expression in the cell-free assay, the PS-modified form of A311 inhibited only 22% to 28% of VEGF expression in the cell-based assay. Therefore, Uchida et al. disclose only six PS-modified antisense probes; all these probes have poor effect for use in cells or in vivo in contrast to the instantly claimed antisense sequences.

Furthermore, the Declarations of Dr. Gill and Dr. Zhang note that the cell-based assays of Uchida et al. were performed at an exceptionally high concentration of phosphorothioate modified probe. While the cell-free assays were performed with 0.4 micromolar concentrations of antisense nucleic acids, the cell-based assays were performed at a 50-fold higher concentration of 20 micromolar. According to both experts, the concentration of 20 micromolar is so high as to create non-specific results in many instances. And yet, despite the high concentration, none of the six phosphorothioate modified probes tested by Uchida et al. had a strong effect on VEGF expression in cells, further indicating the apparent ineffectiveness of the Uchida probes in cells.

Accordingly, Applicants remind the Examiner that the question at issue is not what the Examiner would conclude from a review of the prior art but what one of ordinary skill in the art would conclude from a review of the prior art, and what modifications to the prior art one of ordinary skill in the art would be motivated to make. As described above, Dr. Gill and Dr. Zhang testify in their Declarations that the Uchida antisense probes were ineffective to suppress VEGF expression in cells based assays. Their Declarations provide evidence that a practitioner in the field would not be motivated to create probes of the present claims in view of the teachings of Uchida et al. Per MPEP 2144.08(B), "[o]ffice personnel should consider all rebuttal arguments and evidence presented by applicants." MPEP Eighth Edition, Incorporating Revision No. 2, May, 2004. The Examiner has provided no other factual evidence to establish how one of ordinary skill in the art would interpret the teachings of Uchida et al.

Further, Applicants respectfully submit that Courts have cautioned against the use of the patentees disclosure as a blueprint to reconstruct the invention from the prior art. See *Interconnect Planning Corp. v. Feil*, 227 USPQ 543 (Fed. Cir. 1985). Applicants' specification teaches that the instantly claimed PS-modified antisense probes effectively inhibit proliferation of cancer cells such as Kaposi's Sarcoma cells. See Examples 3-9 at pages 19-25. However, there is no teaching, disclosure, or suggestion of these properties of the PS-modified antisense probes in the Uchida reference. Accordingly, the teachings of the Uchida et al. fail to provide

any reasons for the combination suggested by the Examiner. It is Applicants' position that the Examiner has used improper hindsight in using the disclosure of the Uchida as part of the rejection under 35 U.S.C. § 103(a).

In addition, Applicants submit that Robinson et al. fail to bridge the gap between the teachings of Uchida et al. and the instantly claimed invention. Robinson et al. merely describe in general that synthetic oligonucleotides may include PS modifications. However, it was known in the art that PS-modified antisense probes have unpredictable activities, which is evidenced by the fact that the majority of clinical studies with PS antisense have been disappointing. See, e.g., Agrawal and Kandimalla, 2004, Nature Biotechnology, 22:1533-1537 (enclosed herewith as **Exhibit A**). The specific sequence features of PS antisense oligonucleotides, such as the CpG dinucleotides, may significantly influence (positively or negatively) the desired antisense effect (see, e.g., **Exhibit A**, page 1536, right column, lines 12-23). Because Uchida et al. do not disclose the sequences of the instantly claimed antisense probes or teach how to modify the antisense probes with PS moieties, the vivo efficacy of the instantly claimed PS modified antisense probes could not possibly be appreciated by Uchida et al. considering the unpredictable activity of the PS antisense probes. Applicants remind the Examiner that it is well settled law that "[o]bviousness cannot be predicated on what is unknown." *In re Spormann,* 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

In sum, given that none of SEQ ID NOs: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29 are disclosed literally in Uchida et al., it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida et al. any motivation to make those particular sequences and to further modify these oligonucleotides with phosphorothioate for use in vivo as claimed in the present invention.

B. Failure to provide the Claimed Invention

It is Applicant's position that the proposed combination of references fails to teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q 494, 496 (C.C.P.A. 1970). The claims as currently amended require two key elements: (1) the exact nucleic acid sequences (e.g., SEQ ID NOs: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29); and (2) a plurality of phosphorothioate moieties in these nucleic acids.

Although certain of Applicants' sequences fall within the region defined by Uchida's SEQ ID NO: 7, Uchida et al. do not disclose any of the claimed antisense nucleic acids. In addition, Uchida et al. do not teach how to design other antisense nucleic acids. Theoretically, there can be hundreds of thousands of antisense sequences that may overlap or be embraced in the region defined by Uchida's SEQ ID NO: 7. As a result, one of ordinary skill in the art would recognize that Uchida et al. provide no meaningful guidance for the selection of antisense probes for use in cells or in vivo.

Further, Uchida et al. do not disclose the modified forms of these exact nucleic acids which comprise a plurality of PS moieties. Applicants submit that Robinson et al. fail to overcome the deficiencies of Uchida et al. Even if one accepts the predictions regarding regions based on the Uchida's in vitro assays (which there is substantial reason to doubt), it does not appear that these predictions transfer to the cellular setting or to phosphorothioate modified probes. Therefore, one of skill in the art would not be able to discern any particular variant sequences to be made on the basis of Uchida et al. and to further modify these variant sequences with phosphorothioate.

In sum, the references cited by the Examiner teach either different antisense sequences or modification of antisense molecules with PS in general. The cited references fail to teach or suggest, singly or in combination, the specific PS-modified antisense molecules as currently claimed. Therefore, the proposed combination of the cited prior art fails to teach each and every limitation of the claimed invention.

For the reasons of record and those set forth herein, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 21-23 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 21-23 as being allegedly obvious over Uchida et al. (U.S. 6,150,092), Robinson et al. (5,814,620), Barleon et al. (Blood, 87:3336-3343, 4/15/1996), and Chan et al. (Am J Surg Pathol, 22:816-826, 1998). Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that because Barleon et al. teach inhibition of VEGF via specific antiserum and the role of flt-1 with VEGF biopathway, and Chan et al. teach that the association of VEGF and its receptors and their roles in various diseases, "it would have been obvious to use antibodies in conjunction with antisense targeted to VEGF" (see Office Action, at pages 5-6).

Applicants have provided arguments above that the combination of Uchida et al. and Robinson et al. fails to provide motivation or reasonable expectation of success and fails to provide the claimed invention. Applicants submit that Barleon et al. and Chan et al. merely disclose regulating VEGF protein activity (e.g., by VEGF antibodies). Neither of these references suggests or teaches inhibiting VEGF expression at the transcription/translation level (e.g., by antisense molecules) as claimed in the present invention. In addition, these two references do not suggest or teach combination of two or more approaches for inhibiting VEGF expression and activity as claimed herein. Assuming *arguendo*, these two references were to be combined with Uchida et al. and Robinson et al., they still fail to overcome the deficiencies of Uchida et al. and Robinson et al. because they do not teach or provide motivation to make the instantly claimed PS-modified antisense molecules.

To conclude, Applicants submit that all of the pending claims are non-obvious in view of Uchida et al. Further, since none of the defects of Uchida et al. are cured by the other cited references, Applicants assert that the claims are not obvious in view of all cited references. Applicants believe that a factual basis supporting a finding of non-obviousnesshas now been established, based on opinion of experts in the field. Applicants request that the Examiner either accept the facts as presented or provide a reason for refusing to consider the opinions of these experts. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103(a).

## CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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